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Filed : **February 1, 2002**

REMARKS

Claims 40-44 are pending in the present application. Applicants respond below to the specific rejections raised by the Examiner in the final Office Action mailed November 25, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 101 - Utility

The Examiner maintains the rejection of Claims 40-44 under 35 U.S.C. § 101 as allegedly lacking a specific, substantial, and credible utility for the reasons set forth in the previous Office Actions. The Examiner cites to portions of Applicants specification that relate to the utilities of PRO444 polypeptides as "[(1)] diagnostic markers for particular types of pericyte-associated tumors. . .[(2)] giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. . . [and (3) for] the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing." *Office Action* at 3-4, citing *Specification* at 142. Regarding the first asserted utility, the Examiner maintains that there is no disclosure that PRO444 is exclusively present/absent or expressed at altered levels in pericyte-associated tumors, and concludes that the data are insufficient to establish the utility of PRO444 polypeptides as diagnostic markers. Regarding the third asserted utility, the Examiner maintains that "the evidence presented in the instant specification is inadequate to support a conclusion that PRO444 induced activation of expression of *c-fos* in pericytes is specifically related to angiogenesis," and concludes that the data are insufficient to establish the utility of PRO444 polypeptides to induce angiogenesis. The Examiner states "[t]herefore, the Examiner maintained that two of [the three of] Applicants' originally presented utilities (as a marker for pericyte-associated tumors and for induction of angiogenesis in wound healing, for example) were not supported by the instant specification as filed." *Office Action* at 4, emphasis added..

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject

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matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, <u>any reasonable use</u> that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." If an applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established. M.P.E.P. § 2107.02 (I).

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Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

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The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test

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> results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Applicants assert they have provided reliable evidence that PRO444 stimulates *c-fos* in pericytes. Further, Applicants' specification and evidence of record establish that there is at least a "reasonable correlation" between *c-fos* induction in pericytes and angiogenesis. At the time the application was filed, pericytes were known to be involved in angiogenesis. The Examiner agrees that "pericytes are reasonably expected to play a significant role in the formation of new blood vessels or angiogenesis." *Office Action* at 4. Although the Examiner maintains that there is "no information available at the time of filing regarding their specific role in angiogenesis," (*Id.*), Applicants assert that the previously submitted scientific references demonstrate that pericytes are present in newly formed capillary sprouts, and were known to be involved in later stages of angiogenesis, including survival of newly formed vasculature, for example by secretion of VEGF, as discussed below. As stated by the Examiner, the art at the time of filing also demonstrates that "the role of angiogenic factor VEGF [was] well established" and that "there is no dispute that the art at the time of filing discloses that pericytes could secrete VEGF." *Office Action* at 5. Applicants also maintain that it was well known at the time the application was filed that VEGF expression is regulated by AP-1, a transcription factor comprising *c-fos* and Jun heterodimers. Despite the scientific evidence provided by Applicants, the Examiner nevertheless maintains that "the relationship between *c-fos*, AP-1 and VEGF expression is not obvious." *Office Action* at 5. As discussed below, Applicants have demonstrated that more likely than not, the skilled artisan would believe that PRO444, as a stimulator of *c-fos* in pericytes, would be

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useful as a therapeutic target for pathological angiogenesis, as well as a tool for stimulating angiogenesis.

Section 2107.02 of the M.P.E.P. states that in order to show that an Applicants' asserted utility does not meet the statutory requirement, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art." As shown below, the Examiner has not offered evidence "sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art." Applicants understand the Examiner to be making the following arguments in support of her position that in light of the totality of the evidence of record, Applicants' asserted utilities for PRO444 would be considered "false" by a person of ordinary skill in the art:

1. The Examiner argues that there is no evidence of the specific role of pericytes in angiogenesis, and cites Ozerdem et al. for the proposition that "it is presently not fully understood whether stimulation of pericytes results in up-regulation or down-regulation of vascularization." *Office Action* at 4-5.

2. The Examiner argues that there is no evidence that induction of *c-fos* leads to increased VEGF expression, and asserts that Sakurai et al. and Otani et al. demonstrate that some factors that stimulate *c-fos* do not stimulate VEGF expression or angiogenesis. The Examiner asserts that in view of Sakurai, a skilled artisan would conclude that Applicants' data does not provide any meaningful evidence that PRO444 could be used as a therapeutic in the treatment of pathological angiogenesis.

As discussed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Further, Applicants submit that *even if* the PTO met its initial burden, Applicants have provided rebuttal evidence establishing that more likely than not, a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility of PRO444 as a target for tumor therapy, and as a stimulator of angiogenesis, is true.

As detailed below, contrary to the Examiner's assertion, the art at the time of filing demonstrated specific roles of pericytes in angiogenesis, including involvement in capillary sprout formation (stimulation of endothelial cell (EC) proliferation) and survival of newly-

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formed vessels. The Examiner agrees that the art at the time of filing also established that pericytes secrete VEGF. Further, the Examiner agrees that at the time of filing, it was known that VEGF was important in angiogenesis. Specifically, the references cited below demonstrate that VEGF functions as a potent angiogenic factor, and is closely involved in tumorigenesis due to its mitogenic stimulation of endothelial cells (EC's), as well as functioning as a survival factor for newly formed vessels. Finally, the references at the time of filing had also established that VEGF expression is regulated by *c-fos*.

Applicants submit that the only evidence offered by the Examiner in support of the instant rejection of Applicants' asserted utilities, i.e., Orlandi et al., Sakurai et al. and Ozerdem et al., demonstrates *c-fos* induction in pericytes is involved in angiogenesis and that *c-fos* regulates VEGF expression, and therefore illustrates the soundness of Applicants' asserted utilities.

Pericytes have an established, specific role in angiogenesis

Applicants maintain that several pre-filing references illustrate the state of the art regarding pericyte control of angiogenesis at the time the application was filed, and demonstrate the specific role of pericytes in angiogenesis.

Nehls et al. (1992) *Cell Tissue Res.* 270:469-474 describes pericyte involvement in capillary sprouting during angiogenesis *in situ*. The authors induced angiogenesis in mouse mesentery tissue and used immunofluorescence to identify pericytes. The authors found that pericytes were regularly positioned at and in front of the advancing tips of endothelial sprouts, and bridging gaps between the leading edges of endothelial sprouts. The authors concluded that pericytes are involved in capillary sprouting.

Rhodin et al. also found that pericytes are regularly found in association with capillary sprouts. Rhodin et al., (1989), *J. Submicrosc. Cytol. Pathol.* 21:1-34, 12. As such, the results of Rhodin reinforce the conclusions reached by Nehls, *i.e.*, that pericytes are involved in capillary sprouting.

Diaz-Florez et al. is a review article, dated prior to the filing date of the present application, that summarizes the state of the art regarding pericytes and angiogenesis. Diaz-Florez et al., (1994) Histol. Histopath. 9:807-843. Diaz-Florez was originally offered by the Examiner in support of her argument that the involvement of pericytes in angiogenesis is not fully understood and is "controversial." *See, Office Action* mailed July 21, 2005 at 3. Diaz-

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Florez unambiguously demonstrates that at the time of filing, pericytes had known, specific roles in angiogenesis.

> The abstract of Diaz-Florez lists the following "events" in neovascularization:
>
> a) endothelial cell (EC) *and pericyte activation*; b) basal lamina degradation; c) *migration and proliferation of EC and pericytes*; d) formation of a new capillary vessel lumen; e) *appearance of pericytes around the new capillaries*; f) development of a new basal lamina; g) capillary loop formation; h) persistence or involution, and differentiation of the new vessels; and i) capillary network formation and, eventually, organization into larger microvessels. (emphasis added)

Although Diaz-Florez *et al.* states that angiogenesis is "complex," and that "*stepwise*, the current model of angiogenesis is controversial," Diaz-Florez *et al.* makes it abundantly clear that at the time the instant application was filed, pericytes were known to be involved in several specific steps of angiogenesis. The passage of Diaz-Florez et al. previously cited by the Examiner as demonstrating that the role of pericytes was "controversial," states that "*most of the authors* are of the opinion that the involvement of capillaries with pericytes occurs at the end of the proliferative stage," (*Id.* at 818), which Applicants submit is addressed in studies demonstrating the role of pericytes and VEGF in survival of newly formed vasculature, discussed further below. The same passage of Diaz-Florez describes the "controversy" over the role of pericytes in angiogenesis, previously argued by the Examiner as demonstrating that the role of pericytes in angiogenesis was not understood at the time the instant application was filed. Briefly, studies had demonstrated that in addition to their role in the survival of newly formed vasculature, studies had also shown that pericytes played an early role angiogenesis. The studies referred to in Diaz-Florez showed "fusion of pericytes with the endothelium at the point of active angiogenesis. . .and the presence of cytoplasmic processes of pericytes and EC caving in on each other. . .in the early stages of neovascularization. . .[and] nascent pericytes showing cellular processes advancing at the tips of endothelial sprouts. . .suggesting that pericytes may serve as guiding structures of EC outgrowth." *Id.* Applicants submit that the Examiner mischaracterized the reference, and that Diaz-Florez establishes that pericytes are specifically involved in multiple stages of angiogenesis such as sprout formation/EC proliferation, and survival of newly formed vasculature. Notably, in the instant Office Action, the Examiner did not address Applicants' assertions regarding the teachings of Diaz-Florez.

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In addition to the pre-filing references discussed above, Applicants previously submitted review articles by Ellis et al. and Balabanov et al. that are generalized discussions of the state of the art, which are based on previous studies. In other words, Applicants maintain that although the review articles are published post-filing, by their very nature, they summarize what was known pre-filing. Further, Applicants maintain that regardless of their publication date, the review articles underscore the truth of Applicants' assertions.

Ellis et al. describe the role of pericytes in angiogenesis as it relates to tumor biology. Ellis, (2002), *Oncology* 16(5):14-22. Ellis explains that "the tumor microenvironment is a caustic one. . .[t]herefore, for these fragile endothelial cells [that represent the new primitive capillary network] to survive, they must be exposed to endothelial cell survival factors. . .Endothelial cell survival factors include pericytes that may stabilize endothelium. . .by secretion of endothelial cell survival factors such as VEGF." Ellis, at 20. Thus, it was known that one of the roles in angiogenesis that pericytes play is to promote survival of newly formed vasculature by secreting VEGF.

Balabanov et al. that summarizes the state of the art regarding the role of pericytes in angiogenesis. Balabanov et al., (1998) *J. Neurosci. Res.* 53:637-644. Balabanov et al. state that "[p]erictyes have been implicated in all three stages of new vessel formation: 1) initiation, 2) sprout extension and migration, 3) maturation and cessation of growth," and notably mention that these functions "are thought to be mediated through. . . vascular endothelial growth factor." *Id.* at 640.

Finally, Applicants turn to the one reference relied upon by the Examiner in support of her position that the totality of the evidence demonstrates that pericytes are not known to have a specific role in angiogenesis, an article by Ozerdem et al. entitled "Early contribution of pericytes to angiogenic sprouting and tube formation." Ozerdem et al. (2003) Angiogenesis 6:241-249. The Examiner asserts that "Ozerdem et al., clearly indicates that it is presently not fully understood if stimulation of pericytes results in up-regulation or down-regulation of vascularization." *Office Action* at 4. Applicants submit that this is a mischaracterization of Ozerdem and Applicants' previous response. Ozerdem et al. studied the composition of angiogenic sprouts by immunofluorescence. The authors found the occurrence of pericyte tubes in early carcinoma tumors, noting the presence of "entire vessels [that] appear to be composed of

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pericyte tubes," and "large numbers of individual pericytes invading the tumors." Ozerdem *et al.* at 243. Ozerdem *et al.* also found "the pericytes and endothelial cells are both present at the growing tip of the vascular sprout." *Id.* The authors conclude that "activated. . .pericytes play an early role in the development of angiogenic sprouts and vessels," and underscore the early participation of pericytes in both physiological and pathological angiogenesis. *Id.* Thus, Ozerdem again reinforces the findings and conclusions in the earlier studies of Nehls, Rhodin and Diaz-Florez.

Furthermore, Ozerdem teaches that "pericytes represent an additional target for treatments designed either to up-regulate (for example in ischemic disorders), or down-regulate (for example in cancer) vascularization." *Id.* at 248. In other words, rather than providing evidence that establishes that the skilled artisan would doubt Applicants' asserted utilities, Ozerdem demonstrates *exactly the opposite*, namely that skilled artisans believe that due to their established role in angiogenesis, pericytes are useful in the exact same capacity that Applicants assert in their specification, i.e., as therapeutic targets for treatments where angiogenesis is desirable (ischemia) or where blocking angiogenesis is desirable (cancer). This unambiguously demonstrates that the skilled artisan would believe Applicants' asserted utilities.

Finally, Applicants previously offered a Declaration by Dr. Mary Gerritsen as evidence in support of the asserted utilities. Dr. Gerritsen testifies that "pericytes help. . .stabilize newly formed blood vessels" and that "pericytes play an in important role in regulating angiogenesis." (Gerritsen Decl., ¶6). Applicants remind the Examiner that "Office personnel. . .must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." M.P.E.P. §21107.01(D). The pre-filing publications of Nehls et al., Rhodin et al. and Diaz-Florez et al., as well as the publications of Ellis, Balabanov et al. and Ozerdem et al. all illustrate the same, specific roles for pericytes in angiogenesis testified to by Dr. Gerritsen. The Examiner has offered no reasoning or evidence that contradicts Dr. Gerritsen's testimony, or establishes that the skilled artisan would have a legitimate basis to doubt the credibility of Dr. Gerritsen's testimony.

All of the evidence of record establishes that at the time the instant application was filed, pericytes were known to be involved in angiogenesis in at least two capacities: endothelial sprout

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formation and survival of newly formed vasculature. Applicants maintain that in view of the above, the Examiner's statement that "there appears to be no information available at the time of filing of [pericyte's] specific role in angiogenesis," is unwarranted.

Applicants demonstrate below that the expression of VEGF by pericyte cells is related to the specific roles of pericytes in angiogenesis, including, for example, endothelial cell proliferation and survival of newly formed vasculature.

VEGF has an established role in angiogenesis

Applicants submit that at the time the Application was filed, VEGF was widely-recognized as an angiogenic factor, playing a central role in pathogenic angiogenesis. Applicants submit herewith and discuss below references that demonstrate the state of the art at the time the application was filed regarding VEGF biology.

At the time of filing of the instant application, studies had demonstrated that VEGF is involved in survival of endothelial cells in newly formed vessels. Alon et al., (1995), *Nat. Med.* 1(10):1024-1028, examined the role of VEGF in retinopathy of prematurity (ROP), a disorder that ultimately results in blindness. It was generally accepted at the time that VEGF caused the abnormal vasoproliferation in ROP. Alon et al. showed that the absence of VEGF during the early stage in ROP resulted in blood vessel regression. Exogenously added VEGF reversed this process. Thus, Alon et al. concluded that VEGF is involved in survival of newly formed vasculature. The studies of Benjamin et al. (1997), *Proc. Nat. Acad. USA* 94:8761-8766, demonstrated this same phenomenon. Briefly, Benjamin et al. showed that shutting off VEGF expression in tumors resulted in regression of preformed tumor vessels. Notably, Benjamin et al. commented that this finding was "critical in the success of many angiogenic and anti-angiogenic therapies." Benjamin et al., at 8675. *See also* Fidler et al., (2000), *Cancer J.* 6(Suppl. 3) S225-236, for a discussion of the role of VEGF in survival of newly formed vasculature.

VEGF is a potent mitogen and a chemoattractant for endothelial cells (EC's). In addition VEGF promotes vascular permeability for EC's. Ferrara, N., (1995), *Breast Cancer Res.* 36:127-137, 127. Early studies demonstrated that VEGF promotes angiogenesis *in vitro*, by inducing confluent microvascular endothelial cells to invade a collagen gel and form tube-like structures. Notably, the study of Otani et al., submitted by the Examiner, states that "VEGF. . .produced by pericytes, induce[s] endothelial cell growth in a paracrine manner indicat[ing] a proliferative

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effect of pericytes." Otani, at 1197. Further, augmented VEGF expression was known to be correlated with vascularization associated with increased tumor growth. (See, Benjamin et al., at 8671, and references cited therein). Inhibition of VEGF production or function was also shown to lead to inhibition of tumor growth. *Id.*, and references cited therein. This activity, in combination with VEGF's known function in mediating endothelial cell survival in newly formed vasculature, discussed below, led to the characterization of VEGF as "the pivotal *in vivo* mediator of. . .pathophysiological angiogenesis." Kolch et al., (1995) *Breast Cancer Res. Treat.* 36:139-155, at 139.

Applicants submit that the references cited above demonstrate that at the time the Application was filed, those skilled in the art appreciated the critical role of VEGF in angiogenesis, as required for inducing proliferation of EC cells, survival of newly formed vasculature, and vascular permeability. The Examiner has not offered any evidence that calls into question Applicants' assertions. Without providing any evidence, the Examiner concludes that "the art at the time of the invention does no [*sic*] substantiate the nexus between stimulation of *c-fos* in pericytes and their involvement, positive or negative, in angiogenesis." *Office Action* at 5. In view of the above, Applicants submit that the totality of the evidence demonstrates the relationship between VEGF expression and the role of pericyte involvement in angiogenesis.

c-fos stimulates VEGF expression

Applicants maintain that at the time the instant application was filed, *c-fos* was known to be part of transcription factor AP-1, and that AP-1 was known to regulate VEGF expression.

In 1990, Tischer et al. analyzed the human gene for VEGF. Tischer et al. (1991), *J. Biol. Chem.* 266(18):11947-11954. The authors found that the promoter region for hVEGF contains several AP-1 binding sites, suggesting that *c-fos* is a regulator of VEGF expression. Tischer at 11953. Similarly, the structure of the mouse VEGF gene revealed "multiple consensus binding sties for AP-1." Shima, et al., (1996) *J. Biol. Chem.* 271(7):3877-3882, 3882. Further, in Kolch's review "Regulation of the expression of the VEGF/VPS and its receptors: role in tumor angiogenesis," Kolch summarizes the state of the art at the time by noting "[a]t present, **a comprehensive assessment of several studies highlights the AP-1 transcription factor as an important common denominator for the regulation of VEGF expression**." Kolch, at 144, emphasis added. Kolch highlights various pathways in which both *c-fos* and VEGF expression

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are regulated, including through the Ras and Raf pathways. *Id.* at 144-145. Kolch also links the induction of *c-fos* expression through the Raf and Ras pathways with conversion to a tumorigenic phenotype through activation of VEGF. *Id.* at 145.

Applicants submit that the references discussed above demonstrate that at the time the instant application was filed, those skilled in the art appreciated the role of *c-fos* in VEGF expression, and hence, the role of *c-fos* in the angiogenic process, including neovascularization and stabilization of newly formed vasculature.

In response to Applicants' evidentiary showing, the Examiner argues that "the relationship between *c-fos*, AP-1 and VEGF expression is not obvious." *Office Action* at 5. According to the Examiner, there is "no indication that induction of expression of *c-fos* protooncogene that is known to be induced by many cellular stimuli. . .(see Orlandi et al. . .) leads to stimulation of VEGF expression by means of AP-1 transcription factor." *Office Action* at 5-6.

Applicants maintain that the Examiner has not offered evidence that contradicts the well-established fact that *c-fos* is a subunit of the AP-1 transcription factor. In fact, the evidence submitted by the Examiner unambiguously states as much. Citing to a textbook on transcriptional regulators, Janknecht teaches that "the *c-fos* gene encodes a basic region-leucine zipper transcription factor that requires heterodimerization with a member of the Jun family for stable DNA binding. Fos/Jun heterodimers are present in the AP-1 transcription factor." Janknecht at 443. Thus, there is a clear, "obvious" relationship between *c-fos* and AP-1. The Examiner has offered no evidence that would lead the skilled artisan to doubt this relationship.

Likewise, the Examiner concludes that the relationship between AP-1 and VEGF expression is not obvious. Applicants maintain that Kolch et al. establishes that the relationship is "obvious" to those skilled in the art. The "obvious relationship" between AP-1 and VEGF expression is the very basis for Kolch's conclusion that a comprehensive survey of the literature to date demonstrates that "the AP-1 transcription factor as an important common denominator for the regulation of VEGF expression." Kolch at 144.

The only evidence the Examiner offers in support of her position that the relationship between *c-fos* induction and VEGF expression is "not obvious" is Orlandi et al. Orlandi describes *in vitro* experiments to analyze gene expression levels in fibroblast cells. As such,

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Applicants maintain that Orlandi is not necessarily applicable to pericytes, the specific cell type tested in Assay 93, or angiogenesis. Orlandi showed that after addition of 10% fetal calf serum to culture media, VEGF expression was induced in both *c-fos*$^{-/-}$ fibroblast cells and *c-fos*$^{-/-}$ cells constitutively expressing exogenous *c-fos*, and therefore suggested that *c-fos* may not be necessary for VEGF expression. Importantly, in the discussion of the data, the authors of Orlandi discuss the *in vivo* study of tumorigenesis in *c-fos*$^{-/-}$ transgenic mice by Saez et al. (1995) *Cell* 82:721-732. Saez teaches that tumors in transgenic *c-fos*$^{-/-}$ mice "show[] very little external vascularization." Saez at 723. Due to the lack of vascularization, Saez examined the levels of VEGF mRNA in the tumors of the transgenic mice. The authors found that VEGF mRNA levels were 5-10 fold lower in the tumors from the *c-fos*$^{-/-}$ mice compared to tumors from *c-fos*$^{+/+}$ mice. Notably, Orlandi recognized that the *in vivo* studies of Saez contradict their *in vitro* results, thereby calling into question their conclusions regarding the role of *c-fos* in VEGF expression in fibroblasts.

As a whole, the evidence of record establishes that skilled artisans more likely than not believe that *c-fos* is directly involved in VEGF expression. Applicants maintain that the totality of the evidence fails to establish that it is more likely than not that the skilled artisan would believe that *c-fos* regulates VEGF expression, and would not believe that Applicants' assertions are "false."

c-fos activation in pericytes has a specific activity associated with angiogenesis

Applicants next address the Examiner's arguments that there can be no specific function attributable to PRO444 induction of *c-fos* in pericytes since many factors are known to stimulate *c-fos*. *See, Office Action* at 7. The Examiner previously cited several references including Coulon et al., Herrera et al. and Janknecht et al. in support of this proposition. Applicants previously pointed out that none of the above references discusses *c-fos* activation in pericytes, and are thus not relevant to Applicants' asserted utility. The Examiner does not discuss these references in the instant Office Action. Applicants also argued that the fact that more than one stimulus is known to induce *c-fos* does not logically lead to the conclusion that PRO444 cannot have a specific function in pericyte cells, such as VEGF induction. Applicants previously submitted an article by McColl et al., which articulates and supports Applicants' reasoning, stating that "since *fos* is upregulated by [various stimuli including growth factors], VEGF

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expression could also be elevated in response to these stimuli, *as is indeed the case.*" McColl et al., (2004) APMIS 112:463-480, 467 (emphasis added) Thus, Applicants submit that although various factors may stimulate *c-fos*, these very factors are also involved in angiogenesis, tying the role of *c-fos* activation to angiogenesis.

The Examiner also previously cited two references, Sakurai et al. and Otani et al., which address *c-fos* activation in pericyte cells. The Examiner cites to these references again in the instant Office Action as evidence that the skilled artisan would determine that Applicants' data regarding the induction of *c-fos* in pericytes does not provide meaningful or definitive evidence that PRO444 could be used as therapeutics in the treatment of pathological angiogenesis. *Office Action* at 7. According to the Examiner, Sakurai teaches that *c-fos* mRNA is induced by fetal calf serum (FCS) and various prostaglandins, but that only prostaglandin PGD2 affects VEGF expression. The Examiner also maintains that Otani teaches that angiogtensin II stimulates both VEGF and *c-fos* expression in pericytes, but "does not support an assertion that any factor that stimulates *c-fos* expression in pericytes also stimulates expression of VEGF." *Id.*

Applicants previously argued that Sakurai and Otani teach that activation of *c-fos* in pericytes by prostaglandins, VEGF and angiotensin II leads to angiogenesis, and all of these factors have been implicated in pathological angiogenesis. Otani examined the role of angiotensin II in retinal pericytes. Otani found that angiotensin II induces VEGF expression in bovine pericytes, and that pretreatment of pericytes with antisense *c-fos* oligonucleotides blocks the angiogtensin II-induced VEGF mRNA expression. Otani at 1195. Furthermore, Otani teaches that the media from angiogtensin-treated pericytes induces proliferation of endothelial cells. The stimulatory effect of the conditioned media is blocked by anti-VEGF antibodies. Otani at 1196. Thus, Otani concludes that the secretion of VEGF by pericyte cells acts in a paracrine manner to induce proliferation of EC cells. In other words, the authors reported that angiogtensin II stimulated *c-fos* in pericytes, which in turn led to VEGF expression, which in turn leads to endothelial cell proliferation. Otani fully supports Applicants' assertion that the skilled artisan would more likely than not believe that a molecule such as PRO444, which stimulates *c-fos* in pericytes, is useful as a tool to stimulate angiogenesis, and also as a therapeutic target where blocking neovascularization is desirable, e.g., in tumor therapy.

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As stated above, the Examiner argues that Sakurai et al. teaches that *c-fos* was induced by both prostaglandins and fetal calf serum (FCS), but that only PGD_2 affected the expression levels of VEGF mRNA. In light of this, the Examiner asserts that the skilled artisan would not believe Applicants' assertion that polypeptides that stimulate *c-fos* in pericytes are useful in the treatment of pathological angiogenesis or any other clinical conditions. A careful examination of the data presented, as well as the data that was not presented in Sakurai shows that Sakurai in fact provides further evidence that *c-fos* expression stimulates pericytes, for example through the expression of VEGF. As shown in Figures 2A-2C, FCS stimulates pericytes (compare FCS(-) with FCS(+)); *See also*, Figures 2 and 3. PGD_2 also stimulates pericytes in the absence of FCS. Figure 3. Sakurai also teaches that PGD_2- induced *c-fos* mRNA induction is blocked by treatment of the pericyte cells with Q22536 (Figure 8). By contrast, FCS mediated *c-fos* induction is only mildly affected by treatment with SQ22536. As expected, SQ22536 treatment blocked VEGF mRNA induction in PGD_2-treated cells. In other words, blocking *c-fos* induction in turn blocked VEGF induction. The authors did not examine VEGF mRNA levels in FCS-treated cells. Nor did they examine VEGF mRNA levels in pericyte cultures treated with any other prostaglandin. PGD_2 was the only compound that was tested for its effect on VEGF mRNA expression. Therefore, the Examiner's conclusion that "only PGD_2 affected the expression levels of VEGF mRNA" is merely a reflection of the fact that only PGD_2 was tested for its effect on VEGF expression. Sakurai does not show that FCS induction of *c-fos* does not also lead to induction of VEGF mRNA. Importantly, the authors concluded that their findings of PGD_2-induced activation of VEF through the *c-fos* pathway provides an explanation "for the known link between angiogenesis and chronic inflammation," *Id.* at 2780. Thus, contrary to the Examiner's assertion, Sakurai et al. demonstrates that factors that stimulate *c-fos* in pericytes lead to stimulation of VEGF, and angiogenesis.

As shown above, the references relied upon the Examiner as supporting the position that no specific activity can be attributed to PRO444 since other factors are known to stimulate *c-fos* in pericytes, either are not relevant to the issue of whether *c-fos* activation in pericytes is associated with angiogenesis, or alternatively fully support Applicants' position. In the only two references cited by the Examiner which examine *c-fos* activation in pericytes, the authors discovered that *c-fos* induction led to VEGF induction, which led to angiogenesis. Therefore, the

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references cited by the Examiner demonstrate that those skilled in the art would more likely than not believe that PRO444, as an inducer of *c-fos* in pericytes, would promote angiogenesis, and as such is a useful therapeutic target for pathological angiogenesis.

The skilled artisan would believe that indirect regulators of angiogenic factors (VEGF) are useful as therapeutic targets for cancer therapy

As Dr. Gerritsen testified, Applicants submit that "a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes (e.g., PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis." Gerritsen Decl., ¶6. The discussion above demonstrates that at the time of filing of the instant application, those skilled in the art appreciated the role of pericytes in capillary sprout formation and the survival of neovasculature. Further, the art at the time demonstrated that VEGF was expressed in pericytes, and that VEGF is involved in both proliferation of EC cells and in survival of newly formed vasculature. Finally, those skilled in the art appreciated the central role of *c-fos* in VEGF expression. Thus, Applicants submit, and as Dr. Gerritsen testified, a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes would be useful in tumor therapy.

As proof of this principle, in a review entitled "Angiogenesis Inhibitors in Oncology," Ellis states that anti-angiogenic strategies involved, among others, strategies that decrease the activity of specific angiogenic factors (such as VEGF), and strategies that indirectly downregulate activity of angiogenic and survival factors. Ellis et al., (2002) *Oncology* 16(5):14-22. Ellis proposes that "[s]trategies that downregulate the upstream signaling pathways to VEGF and other angiogenic factors may indirectly downregulate VEGF activity and angiogenesis." Ellis, at 20. Applicants submit that Ellis' discussion of various strategies for cancer therapy describes identification of compounds such as PRO444, that act indirectly to regulate the activity of angiogenic and survival factors, such as VEGF, demonstrating that those skilled in the art believe that compounds such as PRO444 are useful in cancer therapy.

Applicants note that the first strategy proposed by Ellis has been demonstrated to be effective. A VEGF-specific antibody, bevacizumab, has been successfully used to treat several cancer types. See, Kirkpatrick, P., (2005), *Nat. Rev. Drug Disc.* S8-S9. Willett et al. report that

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bevacizumab has antivascular effects in human rectal cancer. Willett et al. (2004) *Nature Medicine*, 10(2):145-147.

In summary, Ellis' discussion provides support for Dr. Gerristen's testimony that those skilled in the art would more likely than not believe that factors that induce the expression of *c-fos*, a known upstream regulator of VEGF, are useful targets for tumor therapy.

Conclusion

Applicants submit that the evidence discussed herein establishes that factors capable of inducing *c-fos* in pericyte cells are useful tools for stimulating angiogenesis, and are useful tools in the design of anti-angiogenic therapeutics, for example for tumor therapy. First, Applicants demonstrated that at the time the application was filed, the role of pericytes in angiogenesis – specifically capillary sprout formation and survival of neovasculature - had been established. Applicants also presented evidence that the role of VEGF as a potent angiogenic factor and as a survival factor for newly formed vasculature was established. Further, Applicants also presented evidence that it was known that *c-fos* played a central role in VEGF expression. Taken together, the above evidence establishes that more likely than not, one skilled in the art would have believed Applicants' asserted utilities for PRO444 at the time of filing of the application. As proof of this, Applicants provided evidence that those skilled in the art had postulated that upstream regulators of VEGF are useful targets for tumor therapy, demonstrating that those skilled in the art would believe PRO444, as an upstream regulator of VEGF in pericytes, is useful for angiogenic and anti-angiogenic therapies, such as tumor therapy. Finally, Applicants have shown that the evidence presented by the Examiner regarding *c-fos* activation in pericytes, rather than establishing that PRO444 lacks specific and substantial utility, clearly demonstrates that those skilled in the art accept the theory upon which Applicants' asserted utility rests, *i.e.*, that stimulation of *c-fos* in pericyte cells leads to angiogenesis.

Applicants submit that it is more likely than not that one skilled in the art would believe Applicants' asserted utility for PRO444 antibodies. Applicants respectfully request that the Examiner withdraw the rejection of Claims 40-45 under 35 U.S.C. § 101.

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Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

The Examiner has maintained the rejection of Claims 40-45 as not being enabled since the claimed invention is allegedly not supported by either a specific and substantial asserted utility, or a well-established utility.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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